Alan Goldhammer, PhD
ASSOCIATE VICE PRESIDENT
US REGULATORY AFFAIRS

PhRMA

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Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Comments on Docket No. 00N-1463;
***Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use*: Proposed Rule**

Dear Sir or Madam:

These comments on a Proposed Rule ("Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use"), as published in the *Federal Register*, Volume 65, Number 182, pages 56511-56518 (September 19, 2000) are submitted on behalf of the Antibiotic Working Group of the Pharmaceutical Research and Manufacturers of America (PhRMA). This Working Group consists of representatives from PhRMA-member companies with historical and ongoing activities in the discovery, development, manufacturing, and distribution of anti-infective drug products. The Antibiotic Working Group has endeavored to provide thoughtful and constructive comments in recent years on FDA's series of guidances for development of anti-infective drug products (see the letter from PhRMA to Docket No. 98N-0517 dated January 29, 1999) and on the interagency task force document on antimicrobial resistance (see the letter from PhRMA to FDA dated August 15, 2000). The enclosed comments are a logical extension of our previous comments.

PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. PhRMA member companies are devoted to inventing medicines that allow patients to lead longer, healthier, and more productive lives; our members invest over $26 billion annually in the discovery and development of new medicines. For this reason, PhRMA and its member companies are keenly interested in all aspects of the drug development process, including the format and content of prescription drug labeling. We appreciate the opportunity to provide comments on this Proposed Rule.

Overall, PhRMA supports public policies that appropriately mitigate antibacterial resistance. However, PhRMA is concerned that the language in the Proposed Rule is, in certain cases, restrictive and not reflective of currently acceptable treatment practices. Although the proposed labeling is consistent with the goals included in the proposed Public Health Action Plan to Combat Antimicrobial Resistance ("The proposed Action Plan;" 65 Federal Register 38832), PhRMA is concerned that the effective date of the proposed labeling may occur before

structural surveillance; prevention and control goals have been implemented.

Consistent with the collaborative approach suggested in the proposed Action Plan, PhRMA proposes a working meeting with the FDA and other appropriate parties, to learn more about the background of this Proposed Rule and develop action items to address antibacterial resistance. A face-to-face meeting is necessary to better achieve an understanding on the important issues being considered.

The following comments are numbered in accordance with the numbering in the Proposed Rule. The comments are divided into general comments on the most important concepts within the Proposed Rule and specific comments on the various sections of the Proposed Rule.

General Comments

Under the Proposed Rule, Section 21 CFR 201.24 would require new statements in five separate places in the labeling for each prescription antibacterial drug for systemic use. PhRMA believes that this is excessive and, because of the proposed placement of the new statements, may be potentially misleading to the reader. The following comments summarize our views:

Proposed Section 201.24 ("Labeling for systemic antibacterial drug products; required statements")

The Proposed Rule should define "systemic antibacterial drug products"; i.e., does it apply to oral or IV only or both?

Sec. 201.24 (a) (at the beginning of the label)

A statement that inappropriate use of antimicrobial drugs may increase the prevalence of drug resistant microorganisms and may decrease the effectiveness of antibacterial drug products

- FDA proposes to include two standard sentences "at the beginning of the label, under the product name." We object to this because it is in conflict with the current labeling regulation [21 CFR 201.57(e)] that reserves the area immediately following the product name for a boxed **WARNING** or other important safety-related warnings applicable to the specific product. A boxed **WARNING** is reserved for critical safety information, usually based on human data, for prescribers on special problems and safety hazards that may lead to death or serious injury.
- Standard statements on inappropriate use of antibacterial drugs do not merit the extraordinary prominence afforded by appearing directly under the product name. Such placement, in the most prominent location of the label, implies that these statements provide the most important information about the product to merit this prominence both in labeling and as part of the fair balance information in promotional labeling.
- Information on approved **INDICATIONS** (including Description of Clinical Studies), **CONTRAINDICATIONS**, and **WARNINGS** should generally merit greater prominence than statements on inappropriate use. PhRMA recommends that a more suitable location for the inappropriate use information would be in the **PRECAUTIONS** section.

Antibacterial drug products should be used only to treat infections that are proven or strongly suspected to be caused by susceptible microorganisms

- Many infections for which antimicrobial drugs are prescribed in the outpatient setting affect the respiratory tract, where specimens for culture and susceptibility testing are not routinely obtained (e.g. pharyngitis, otitis media, and bronchitis).
- The trends away from obtaining cultures for isolation and susceptibility testing have been prompted by a shortsighted attempt at cost-containment, which has reduced the availability and practicality of diagnostic testing in primary care, leading to reliance on broad-spectrum antimicrobials to "cover all bases."
- For ambulatory patients with acute respiratory tract infections, focus is directed toward respiratory infections and susceptibility data that are rarely available at the time prescriptions are written. Currently, there are no rapid diagnostic tests available at most points of care that will reliably distinguish viral from bacterial infections, or distinguish susceptible from resistant bacterial pathogens. In many cases, withholding antibiotics or requesting a second office visit is not feasible, nor is it standard practice for patients with mild or moderately severe infections. Therefore, it is difficult for a practicing clinician to make judgments about the "best" antimicrobial agent for the patient at the time treatment is indicated. In patients at risk of serious complications from infections, empiric antimicrobial therapy is indicated, and broad-spectrum therapy may be prescribed to avoid treatment failures.
- The "Summary" section in the Proposed Rule states that physicians are being "encouraged" to "prescribe systemic antibacterial agents more judiciously and only when clinically necessary." It is important to recognize the expertise and experience of physicians and their ability to use this background to determine clinical necessity when prescribing antibacterial agents. Clinical practice and the experience of the physician provide the clearest rationale for prescribing practice and the use of this knowledge does not constitute "inappropriate use."
- Outside of pharmaceutical industry-sponsored clinical trials and surveillance studies, there are few coordinated efforts to gather information on the outcomes of treatment for infections in the ambulatory care setting, and to determine the exact costs of current prescribing practices. These efforts may assist in providing inappropriate use information to help determine background in this area.

Based on the above-mentioned documents, PhRMA recommends the following language:

"Antibacterial drug products should be used for the appropriate treatment of infections that are suspected or proven to be caused by susceptible microorganisms."

Sec. 201.24 (b) ("Clinical Pharmacology") and (c) ("Indications and Usage")
General Comments

- The statements proposed for inclusion in the **CLINICAL PHARMACOLOGY** and **INDICATIONS AND USAGE** sections (201.24 (b) and (c)) are not appropriate for the following reasons:
    (a) The call for universal identification of causative microorganisms conflicts with some current treatment guidelines (e.g., guidelines provided by the American Thoracic

Society and Infectious Diseases Society of America for treatment of community-acquired pneumonia in outpatients[1-2]),

(b) The emphasis on microbiological studies ignores the reality that the regulations of the Clinical Laboratory Improvement Act discourage physicians from examining sputum microscopically (also, the Infectious Diseases Society of America, the Canadian Infectious Disease and Thoracic Society, and the American Thoracic Society in its "Pneumonia Guideline" recommend against routine sputum culture as part of routine management of out-patient pneumonia; the approach of culturing microorganisms as part of the treatment of out-patient infections is not practical or cost-effective in the clinical setting and is still a subject of debate in the scientific community),

(c) The call for use of "local epidemiology and susceptibility patterns" is difficult to implement in practice (there is not scientific consensus on the need to use narrow spectrum antibiotics targeted to organisms that have been identified through cultures),

(d) The proposed statements deviate from the long-standing practice of FDA to grant indications for each specific infection that was studied in adequate and well-controlled trials, and

(e) The proposed statements are required, inappropriately in our view, both for antibacterial drugs intended for use in ambulatory care and for antibacterial drugs intended for use in hospitalized patients.

Finally, this Proposed Rule does not recognize that antibiotic use for prophylaxis of bacterial infection in some settings is an FDA-approved and valuable clinical use of several antibacterial drugs; the labeling suggested by this Proposed Rule would be inconsistent with such prophylactic use. Therefore, for these reasons, the labeling proposed for these sections may add questions of liability, additionally constraining the decision-making process and compromising the physician's role as the primary and best-informed decision-maker.

Sec. 201.24 (b) ("Clinical Pharmacology")

Susceptibility testing of isolated pathogens should be done when possible to guide the choice of an antibacterial drug product

- The infrastructure required to support diagnostic testing in primary care settings is currently not in place and is unlikely to be funded without data to support the cost-effectiveness of having culture and susceptibility data to guide antimicrobial therapy (compared with the choice of a broad-spectrum antimicrobial agent).
- Without additional support for diagnostic microbiology services, it will only rarely be possible to perform susceptibility testing on pathogens from ambulatory patients to guide decisions on choice of antimicrobial agents.
- The pharmaceutical industry should not be obligated to provide or support the establishment of diagnostic microbiology services for patient care since it is only one contributor to the total health care delivery system. Such services must first be shown to be necessary and cost-effective for certain patients by health care professionals and payors, then diagnostic laboratories must explore efficient means to provide such services.
- The meaning of "where applicable" in reference to performing culture and susceptibility testing is unclear and subject to variable individual interpretation.

- Further, inclusion of susceptibility data in the label begs the question, "Which susceptibility data?" As pointed out in the proposal, local epidemiology and susceptibility patterns provide very important information. There are various sets of susceptibility data available, with datasets that include multiple local sites and national and international data. Inclusion in product labeling of different sets of data, collected at different times from differing clinical settings, makes meaningful interpretation very difficult. Also, susceptibility profiles of key pathogens can change relatively rapidly, which can make certain data obsolete as soon as it is collected and analyzed.

Sec. 201.24 (c) ("Indications and Usage")
Initial selection of an antibacterial drug product should be based on local epidemiology and susceptibility patterns of suspected or identified microorganisms

- Prescription antibacterial drugs are licensed for marketing in the United States only after substantial evidence of efficacy and safety is demonstrated in adequate and well-controlled clinical trials. A favorable benefit/risk profile for the drug must be demonstrated in patients with documented bacterial infections. It is not appropriate to extrapolate this benefit/risk profile from patients with documented bacterial infections to other patient populations (e.g., patients with viral infections). In some clinical trials, treatment is initiated empirically based on suspected bacterial etiology and results of cultures are typically reported 24-48 hours later. It is important to note that routine clinical practice dictates empiric prescribing, particularly for such common ailments as otitis media in children; susceptibility testing is not routinely performed in this setting.
- The lack of susceptibility data on any given product in a specific geographic region should not be used as a reason to contraindicate the use of that antimicrobial agent or class of antimicrobial agents. If resistance problems are suspected based on analysis of treatment outcomes in similar clinical settings (from clinical trials or case series from individual clinicians) then new antimicrobial options should be put into practice while susceptibility data are being collected, so that potential problems with the emergence of resistance can be effectively curtailed.
- To improve the quality of available data, a coordinated effort should be initiated involving local health authorities, hospital and outpatient clinics, pharmaceutical industry-sponsored programs, and managed care organizations. Such collaborations are endorsed in the proposed CDC guidelines.

PhRMA recommends that this section of proposed labeling be dealt with as follows:

"The efficacy of this drug has been demonstrated when it is used as directed for the indications and susceptible pathogens listed below. Use of this drug in other regimens or for other indications or pathogens may be ineffective. Inappropriate use of this or other antibacterials may increase the prevalence of drug resistant microorganisms."

Definitive therapy should be guided by the results of susceptibility testing of isolated pathogens

- Efforts to obtain and facilitate the review of available microbiology data and to encourage the selection of appropriate antimicrobial agents, all by appropriately trained specialists, are warranted.
- Peer-review of antimicrobial use and prescribing practices is preferred over static treatment guidelines and restrictions, given the complexity of the decision-making process faced by individual clinicians when evaluating individual patients.
- Realizing that (a) cultures are not obtained as part of routine care in many settings and (b) observed culture results may be affected by prior antimicrobial therapy selection, handling of specimens, and specimen processing by the laboratory, the availability and quality of laboratory data generated for an individual patient may vary widely. When available, data should be analyzed by trained personnel prior to making treatment decisions, developing guidelines, or initiating formulary changes.

Thus, PhRMA recommends that the following language is appropriate for inclusion on the drug label:

"The prescription of antimicrobial therapy should be guided, when possible, by the results of local or regional susceptibility testing of causative pathogens typically isolated during the infection. When microbiological data are not available for an individual patient, the decision to prescribe an antibiotic should be based on the clinician's assessment of the most likely etiology and optimal therapy based on the available clinical, pharmacodynamic, and in vitro information provided from clinical trials and post-marketing experience with antimicrobial agents."

Sec. 201.24 (d) ("Precautions" - General)

Inappropriate use of antibacterial drug products may increase the prevalence of drug resistant microorganisms and may decrease the future effectiveness of antimicrobial agents

- Appropriate use of antimicrobial agents may also carry similar risks, if patients are non-compliant with the full course of therapy or otherwise alter the prescribed dosing regimen.
- PhRMA agrees that any use of antimicrobial agents, even appropriate definitive therapy, may increase selective pressure that favors the emergence of resistant microorganisms. However, decreased effectiveness is a greater clinical concern in empiric therapy when microbiological data for a given patient are not readily available[3]. The spread of microorganisms, including resistant organisms, through breakdown in basic infection control practices and hygiene measures (e.g. handwashing, vaccination/immunization programs, and adequate personal care in day care centers for children and elderly adults) is more likely to have contributed to the dissemination of resistant organisms than the individual misuse of antimicrobial drugs[4].
- Prescribing the incorrect dose of an appropriate drug may also contribute to potential risk for development of resistance. Physician education in the appropriate dosing of antimicrobial drugs needs to be a continuing medical education priority.
- Generic antibacterial drug products should be held to the same standards as patented products, and their labeling should carry the same instructions regarding dosing, duration of treatment, and important information regarding bio-equivalency differences, if any have been observed.

In Section 201.24 (d), PhRMA supports inclusion of the following statements in this subsection of labeling:

> *"Inappropriate use of an antibiotic may increase the prevalence of drug-resistant microorganisms and may decrease the future effectiveness of the antibiotic and related antimicrobial agents. It is not appropriate to extrapolate the benefit/risk profile established in patients with documented bacterial infections to other patients (e.g., patients with viral infections). This antibiotic does not treat viral infections."*

Sec. 201.24 (e) ("Precautions" – under "Information for patients")
There is a need to educate patients about when and how to take antibiotics, including the following:

- Antibacterial drug products are not effective against viral infections: PhRMA agrees with this statement, but believe that patient information should primarily reinforce dosing as prescribed and approved in the label. The patient should not be expected to know how to distinguish bacterial from viral infections without the evaluation and advice of a health care professional.
- Not taking a medication exactly as directed may decrease the effectiveness of the immediate treatment or increase the likelihood that bacteria will develop resistance to it.
  1. Compliance with the prescription should be emphasized to optimize the benefit and minimize the risks of therapy with antimicrobial agents.
  2. There is a need to educate patients about the need for at least one office visit to decide whether antimicrobial drugs are indicated and, if so, which to prescribe. This would also provide an opportunity for clinicians to encourage follow-up for significant changes in the patient's condition.
- In Section 201.24 (e), PhRMA supports providing information to the patient on the premise that the decision to prescribe has been made. The following statement should be included in this subsection of labeling:

> *"Patients should be counseled that the oral antibiotic should be taken exactly as prescribed. Patients should be told that skipping doses or not finishing the full course of antibiotic may (1) decrease the effectiveness of their treatment and (2) increase the likelihood of selecting bacteria that will not be treatable by this antibiotic in the future."*

Specific Comments

Section I.A. Factors Contributing to the Emergence of Resistance:
FDA cites the 1992 survey by Gonzales *et al.* (*JAMA*, 1997) that reported that approximately 21% of all antibiotic prescriptions for adults were written to treat respiratory infections that were thought to be viral in etiology. Clearly, such prescribing is inappropriate for patients with infections of viral etiology that lack a concurrent bacterial component. However, empiric therapy, as we have noted above in several places, is a necessary part of contemporary medicine

and it enables physicians to provide effective therapy for the vast majority of bacterial infections even when no bacterial cultures are or will be available.

PhRMA recommends that FDA consider collaborating with other stakeholders (such as the American Medical Association, in addition to PhRMA-member companies) to foster education of prescribers, as well as the American public, about appropriate non-antibacterial interventions for the common cold, viral upper respiratory infections, and viral bronchitis. Such an active educational effort might go a long way toward encouraging appropriate non-antibacterial treatment, while discouraging inappropriate use of antibacterial drugs. It is also of great importance to determine how patient compliance might be enhanced and to develop programs to achieve this.

Section I.B. Responding to the Resistance Problem:
The first sentence of this section states that "*Bacterial resistance can be reduced by decreasing the use of antibacterial drugs.*" PhRMA suggests that this statement would be better aligned with FDA's Proposed Rule if it states, "*Bacterial resistance can be reduced by decreasing the inappropriate use of antibacterial drugs.*" Inappropriate use of antibacterial drugs includes use of such drugs to treat viral infections, failure to prescribe an adequate duration of treatment, failure of patients to complete the entire course of treatment, skipping doses, and other factors. It is important that physicians and the public understand the basic value of antibacterial drugs – only inappropriate usage should be highlighted as requiring further education and restraint. Consideration should also be given to soliciting additional academic debate and input from all stakeholders on this subject to assure the widest contribution base. This could provide additional input in the effort to educate the medical and patient population regarding this important topic. "Standard of practice" needs to be recognized in the education process – while it would be nice to know the type of bacteria involved in an illness and its susceptibility pattern, this is not realistic when prescribing antibiotics for the vast majority of bacterial infections.

Section I.C. Scope of the Proposal:
Some of the patient-related factors (e.g., skipped doses, failure to complete the entire course, using outdated drug from previous prescriptions) that foster antibacterial resistance also foster development of resistance of *Mycobacterium* species to drugs. Therefore, once comments on this Proposed Rule are considered and a Final Rule is issued for antibacterial drugs, it seems reasonable to apply the same principles to antimycobacterial drugs. PhRMA would emphasize the importance of the use of topical antibiotics/antiseptics in resistance development and their possible inclusion in a future proposal. Further patient/public and practitioner education about resistance and the proper prescribing and use of antibacterial agents is an excellent undertaking and PhRMA wishes to work with FDA to successfully implement this initiative.

Section V.A. Benefits:
This section of the preamble provides the Agency's estimate of the direct and indirect costs of infections due to resistant bacteria. Understandably, this section examines several reports of the increased societal costs of drug-resistant bacterial infections and estimates the savings associated with reduction in inappropriate use of antibacterial drugs. However, and importantly, the analysis does not examine the cost of the other possible outcome of this Proposed Rule, i.e., an

increased frequency of prescribers not initiating or delaying initiation of antibacterial therapy for a suspected bacterial infection. In such situations, out of concern about inappropriate use of an antibacterial drug, the prescriber may elect not to empirically initiate an antibiotic while awaiting results of culture and susceptibility testing; in some patients, this delay in initiation of an antibiotic can lead to worsening of infection, increased likelihood of complications, or an increased frequency of poor outcomes. In managed care environments, this delay in initiation of an antibiotic may lead to increased costs due to more follow-up visits. In some practice settings, prescribers are focused on empiric initiation of antibiotics in an effort to minimize the possibility of worsening infection, complications, and the need for follow-up visits. The costs of not pursuing these outcomes should be estimated and factored into FDA's calculations. This factor is well described in comments of August 2, 2000 provided by the Infectious Diseases Society of America (IDSA) on the "*Public Health Action Plan to Combat Antimicrobial Resistance*"; the relevant paragraph is included below[5]:

> *Much attention is given in the Action Plan to "judicious or prudent use" of antimicrobial agents. IDSA, the Society for Healthcare Epidemiology of America (SHEA), and others prefer the phrase "good antimicrobial stewardship" over "judicious or prudent use." PhRMA prefers the former because we think it is not only important to reserve and withhold antimicrobial agents in appropriate situations, but also equally important to emphasize the tremendous value of using antimicrobial agents appropriately in those situations in which they are indicated. Antimicrobial agents are among the most effective pharmaceutical agents ever developed and have been invaluable in curing infections, decreasing morbidity and saving lives. Practicing good antimicrobial stewardship encompasses both of these aspects of antimicrobial use. Practitioners are the stewards of these valuable agents and in using them must consider not only the risks and benefits to the immediate patient being treated, but also the more global effects of such usage on microbial resistance.*

Effective Date and Proposed Implementation Plan

FDA proposes that any final rule based on this Proposed Rule become effective 1 year after the date of its publication in the Federal Register. After that date, new drug applications (NDAs) submitted under 21 CFR 314.50 and abbreviated new drug applications (ANDAs) submitted under 21 CFR 314.94 for systemic antibiotic drug products intended for human use (except those intended to treat mycobacterial infections) would have to comply with the labeling requirements under proposed Sec. 201.24.

Holders of approved NDAs or ANDAs would be encouraged to make the labeling changes prior to the effective date of the final rule and would submit supplements that do not require preapproval under 21 CFR 314.70(c) or 21 CFR 314.97. Holders of pending applications would submit amendments under 21 CFR 314.60 or 21 CFR 314.96. To streamline the agency's review, these supplements and amendments would include only the labeling changes proposed in this rulemaking.

PhRMA is concerned that the effective date of the proposed labeling may occur before surveillance, prevention and control goals included in the proposed June 22, 2000 Action Plan have been implemented. Specifically, a key issue identified in the surveillance area is that "the United States lacks a coordinated national plan for surveillance of 1) antimicrobial resistance emergence in organism-drug combinations of public health importance and 2) antimicrobial drug use in human and no-human settings.[6]" To address this structural issue, over 20 action items were developed with implementation dates beginning up to five years from June 2000. Moreover, these objectives were augmented with over 40 prevention and control action items that are also expected to be implemented over the next five years. As the FDA is aware, many of the proposed activities require public and private sector collaboration and may require new federal and state appropriations.

Considering the multitude of factors that may impact the implementation of the goals included in the Action Plan, PhRMA is concerned that delays may occur and significantly impact the successful implementation of the proposed antibacterial labeling. Accordingly, PhRMA recommends that the effective date of the proposed antibacterial labeling should be contingent upon the complete implementation of the surveillance, prevention and control goals identified in the proposed Action Plan.

We trust that these comments are useful as the Agency moves forward with the rulemaking process.

Sincerely,

Alan Goldhammer

References

1. Bartlett JG, Dowell SF, Mandell LA, File TM, Musher DM, Fine MJ. Practice guidelines for the management of community-acquired pneumonia in adults. Clinical Infectious Diseases 31: 347-382 (2000).
2. Niederman MS, Bass JB, Campbell GD, et al. Guidelines for the initial empiric therapy of community-acquired pneumonia: Proceedings of an American Thoracic Society Consensus Conference. Am. Rev. Resp. Dis. 148: 1418-1426 (1993).
3. Levy, S. – Global Resistance Day presentation, ICAAC 40: Toronto, Canada, 9/16/00.
4. Dagan, R. – Global Resistance Day presentation, ICAAC 40: Toronto, Canada, 9/16/00.
5. Letter of August 2, 2000 from the Infectious Diseases Society of America to the Office of Health Communication (National Center for Infectious Diseases, Centers for Disease Control and Prevention) regarding the *Public Health Action Plan to Combat Antimicrobial Resistance.*
6. Draft Public Health Action Plan to Combat Antimicrobial Resistance; p. 12; June 2000.